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**Sinus microbiome diversity depletion and *Corynebacterium tuberculo*stearicum enrichment mediates rhinosinusitis.**

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**Public Summary:**

Persistent mucosal inflammation and microbial infection are characteristics of chronic rhinosinusitis (CRS). Mucosal microbiota dysbiosis is found in other chronic inflammatory diseases; however, the relationship between sinus microbiota composition and CRS is unknown. Using comparative microbiome profiling of a cohort of CRS patients and healthy subjects, we demonstrate that the sinus microbiota of CRS patients exhibits significantly reduced bacterial diversity compared with that of healthy controls. In our cohort of CRS patients, multiple, phylogenetically distinct lactic acid bacteria were depleted concomitant with an increase in the relative abundance of a single species, *Corynebacterium tuberculo*stearicum. We recapitulated the conditions observed in our human cohort in a murine model and confirmed the pathogenic potential of *C. tuberculo*stearicum and the critical necessity for a replete mucosal microbiota to protect against this species. Moreover, *Lactobacillus sakei*, which was identified from our comparative microbiome analyses as a potentially protective species, defended against *C. tuberculo*stearicum sinus infection, even in the context of a depleted sinus bacterial community. These studies demonstrate that sinus mucosal health is highly dependent on the composition of the resident microbiota as well as identify both a new sino-pathogen and a strong bacterial candidate for therapeutic intervention.

**Scientific Abstract:**

Persistent mucosal inflammation and microbial infection are characteristics of chronic rhinosinusitis (CRS). Mucosal microbiota dysbiosis is found in other chronic inflammatory diseases; however, the relationship between sinus microbiota composition and CRS is unknown. Using comparative microbiome profiling of a cohort of CRS patients and healthy subjects, we demonstrate that the sinus microbiota of CRS patients exhibits significantly reduced bacterial diversity compared with that of healthy controls. In our cohort of CRS patients, multiple, phylogenetically distinct lactic acid bacteria were depleted concomitant with an increase in the relative abundance of a single species, *Corynebacterium tuberculo*stearicum. We recapitulated the conditions observed in our human cohort in a murine model and confirmed the pathogenic potential of *C. tuberculo*stearicum and the critical necessity for a replete mucosal microbiota to protect against this species. Moreover, *Lactobacillus sakei*, which was identified from our comparative microbiome analyses as a potentially protective species, defended against *C. tuberculo*stearicum sinus infection, even in the context of a depleted sinus bacterial community. These studies demonstrate that sinus mucosal health is highly dependent on the composition of the resident microbiota as well as identify both a new sino-pathogen and a strong bacterial candidate for therapeutic intervention.

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